Circ J 2008; **72:** 1605 – 1609

Effect of Intracoronary Tirofiban in Patients Undergoing Percutaneous Coronary Intervention for Acute Coronary Syndrome

Tong-Guo Wu, MD; Qiang Zhao, MD, PhD; Wei-Guang Huang, MD;
Jian-Rui Wei, MD; Si-Wei Chen, MD; Jin Zhao, MD;
Li-Ping Huang, MD; Le-Xin Wang, MD, PhD*

Background To investigate the efficacy of intracoronary tirofiban during primary percutaneous coronary intervention (PCI) for patients with acute coronary syndrome (ACS).
Methods and Results The 118 patients aged 70 years and above (average age 75±2) were divided into study (n=58, intracoronary bolus tirofiban) and control (n=57, intravenous tirofiban) groups. The culprit vessels were targeted with primary PCI in all patients. Compared with the control group, the study group showed better Thrombolysis In Myocardial Infarction (TIMI) flow grades and TIMI myocardial perfusion grades (TMPG) immediately after PCI (p=0.016 and 0.026, respectively). The 14-day composite major adverse cardiac events rate was lower in the study group (3.5% vs 17.5%, p=0.030), but was similar between the 2 groups at 30 days following PCI (7.0% vs 1.7%, p=0.350). The left ventricular ejection fraction in the study group was higher than in the control group 30 days following PCI (67.4±6.2% vs 60.7±4.6%, p=0.033). The 14-day bleeding complication (p=0.201) and platelet reduction rates (p=0.984) were similar between the 2 groups.
Conclusion In patients with ACS undergoing primary PCI, intracoronary bolus administration of tirofiban is superior to intravenous bolus injection for improving coronary flow, myocardial perfusion and short-term clinical outcomes. (*Circ J* 2008; **72:** 1605 – 1609)

Key Words: Acute coronary syndrome; Percutaneous coronary intervention; Tirofiban

Several recent guidelines for the management of patients with acute coronary syndrome (ACS) recommend the use of glucoprotein (GP) IIb/IIIa antagonists with primary percutaneous coronary intervention (PCI)[1,2] In most of these guidelines, abciximab is recommended as the drug of choice[1–3] Tirofiban is another IIb/IIIa antagonist that has been found to be less effective than abciximab in platelet inhibition within 60 min of intravenous administration;[4] however, when given by intravenous bolus injection followed by maintenance infusion, tirofiban achieves significant inhibition of platelet aggregation[5] This regimen appears to be safe and effective in high-risk ACS patients treated with primary PCI[6,7]

It is likely that intracoronary administration of a GP IIb/IIIa antagonist will increase the drug's concentration at the site of coronary thrombosis, which may subsequently enhance the binding of the drug molecules to both platelets and endothelium receptors. Preliminary data suggest that intracoronary administration of abciximab offers greater therapeutic effects than intravenous administration[8,9] In the present study, we evaluated the impact of intracoronary tirofiban injection on the short-term cardiac events following primary PCI in patients with ACS. As a recent study suggests that elderly patients may be more likely to suffer from major bleeding complications of GP IIb/IIIa treatment[10] we specifically targeted patients who were more than 70 years old to facilitate the analysis of safety data.

(Received April 18, 2008; revised manuscript received May 13, 2008; accepted May 26, 2008; released online August 28, 2008)
*Department of Cardiology, The Red Cross Hospital of Guangzhou City, Fourth Affiliated Hospital of Jinan University, Guangzhou, PR China, *School of Biomedical Sciences, Charles Sturt University, Wagga Wagga, NSW, Australia*
Mailing address: Le-Xin Wang, MD, PhD, School of Biomedical Sciences, Charles Sturt University, Wagga Wagga, NSW 2678, Australia. E-mail: lwang@csu.edu.au or Tong-Guo Wu, MD, Department of Cardiology, The Red Cross Hospital of Guangzhou City, Guangdong Province 510220, PR China. E-mail: wutongguo@sohu.com

Methods

Patient Selection

This study followed the local ethics guidelines for human research and was approved by the institutional review board of the Guangzhou Red Cross Hospital. Written informed consent was given by all participants before the study.

Between March 2005 and October 2007, 118 patients (72 males, average age 75±2 years) were enrolled in this single-center, open-label randomized study; 78 patients had ST-elevation ACS and 40 had non-ST elevation ACS (Table 1).

The patients were selected from 600 patients consecutively referred for ACS management. Patients were considered eligible if they fulfilled all of the following criteria: (1) angina less than 12 h prior to hospital admission; (2) ≥70 years old; (3) ST-T changes in 2 consecutive ECG leads or more; and (4) cTnT elevation.

Patients who had any 1 of the following conditions were excluded from the study: (1) systolic BP <80 mmHg; (2) GP IIb/IIIa administration within 2 weeks before the study; (3)

Table 1 Baseline Clinical Characteristics of the Patients

	Control (n=57)	Study (n=58)	p value
Age (years)	74.8±1.6	76.4±2.3	0.732
Sex (male)	30 (52.6%)	33 (56.9%)	0.646
Prior MI	3 (5.3%)	2 (3.4%)	0.984
Hypertension	39 (68.4%)	42 (72.4%)	0.639
Diabetes	8 (14.0%)	7 (12.1%)	0.754
Current smoker	20 (35.1%)	23 (39.7%)	0.613
STEMI	36 (63.2%)	36 (62.0%)	0.756
NSTEMI	11 (19.3%)	10 (17.2%)	0.775
LDL (mmol/L)	2.92±0.13	2.68±1.09	0.698
Triglycerides (mmol/L)	1.68±0.38	1.74±0.66	0.624
Time from onset of chest pain to PCI (h)	4.1±1.2	4.2±1.6	0.480
Hospitalization (days)	15.2±6.0	15.1±4.7	0.782

MI, myocardial infarction; STEMI and NSTEMI, ST-elevation and non-ST-elevation myocardial infarction, respectively; LDL, low-density lipoprotein; PCI, percutaneous coronary intervention.

coronary bypass graft within 2 months or PCI within 6 months before the study; (4) undergone thrombolytic therapy within 48 h before PCI; (5) presence of contraindications for anticoagulant therapy, such as severe and uncontrolled hypertension (systolic BP ≥180 mmHg), major surgery or trauma within 6 weeks, hemorrhagic stroke within 6 months, major gastrointestinal bleeding within 6 months; and (6) serum creatinine >2.5 mg/dl or platelets $<60\times10^9$/L.

Study Protocol

Patients were randomized into study and control groups. Patients from both groups were given oral aspirin 100 mg and clopidogrel 300 mg before primary PCI. Unfractionated heparin (5,000 units, IV bolus) was also administered before PCI. In both groups, bolus tirofiban injection was administered after the completion of coronary angiography (CAG), but immediately before angioplasty or stenting of the infarct-related coronary arteries.

In the control group, tirofiban was given intravenously as a bolus (10 μg/kg over 3 min) followed by maintenance intravenous infusion at 0.15 $\mu g\cdot kg^{-1}\cdot min^{-1}$ for 36 h. In the study group, tirofiban was administered as an intracoronary bolus injection (10 μg/kg over 3 min) followed by maintenance intravenous infusion at 0.15 $\mu g\cdot kg^{-1}\cdot min^{-1}$ for 36 h.

After PCI, all patients were managed in the cardiac care unit with once-daily dose of aspirin (100 mg) and clopidogrel (75 mg). Subcutaneous unfractionated heparin (5,000 units, q12h) was administered for 5 days after the PCI. A β-blocker, a statin and an angiotensin-converting enzyme inhibitor (ACEI) were also routinely prescribed to the patients after the PCI.

Evaluation of Therapeutic Efficacy

All coronary angiograms were evaluated by 2 readers without knowledge of the patient's clinical status or treatment. Scores of thrombus in the infarct-related artery were assessed as following: 0: no thrombus; 1: possible thrombus; 2: the length of the thrombus is less than 50% of the vessel diameter; 3: the length of the thrombus is half to twice the vessel diameter; 4: the length of the thrombus is longer than twice the vessel diameter.[11]

Flow in the PCI-targeted coronary arteries was assessed by Thrombolysis In Myocardial Infarction (TIMI) flow grade.[12] The TIMI myocardial perfusion grade (TMPG) was used to assess myocardial tissue-level perfusion.[13] TMPG was assessed only in the area supplied by the culprit vessel. Distal embolism in the targeted vessels was also evaluated following PCI, using the methods reported by Kalaria et al.[14]

Left ventricular ejection fraction (LVEF) was assessed by standard 2-dimensional echocardiography at 14 and 30 days after PCI. Major adverse cardiac events (MACE), such as death, non-fatal myocardial infarction (MI) or reinfarction, revascularization of targeted vessels, or worsening left ventricular dysfunction, were also assessed at 14 days and 30 days following PCI.

Major bleeding was defined as a fall in hemoglobin ≥2.0 mmol/L and the need for transfusion of at least 2 units of blood, or as bleeding that resulted in intracranial hemorrhage, retroperitoneal hemorrhage, or gastrointestinal bleeding. Minor bleeding was defined as a fall in hemoglobin <2.0 mmol/L without the need for a blood transfusion.[7]

Statistical Analysis

Continuous data are expressed as mean values ± SD. Student's t-test was used to analyze continuous variables. Categorical variables were analyzed by chi-square or Fisher's exact test. P-value <0.05 was considered statistically significant.

Results

General Findings

The baseline characteristics of the patients are shown in Table 1. There was no significant difference between the 2 groups in age, sex, ST-elevation ACS or the average time from onset of chest pain to PCI (Table 1). Prior to the PCI, the average CK-MB (1.6±3.3 vs 1.9±4.2 ng/ml, p=0.462) and cTnT (0.24±0.32 vs 0.26±0.41 ng/ml, p=0.778) were similar between the groups.

PCI was unsuccessful in 2 patients from the control group and 1 patient from the study group. Following PCI, all patients in the study and control groups were administered with clopidogrel, a statin and an ACEI. Fifty-six (96.6%) of the study group and 54 (94.7%, p=0.976) of the control group patients were administered a β-blocker.

Results of CAG

As shown in Table 2, there was no significant difference between the 2 groups in the characteristics of the culprit vessels or the use of drug-eluting stents. Before PCI, the average thrombus scores, TIMI flow grade and TMPG were also similar between the groups.

After PCI, the thrombus score in the study group was lower than in the control group (p=0.006), whereas the

Table 2 Angiographic and Procedural Characteristics

	Control (n=57)	Study (n=58)	p value
Culprit vessel			
LAD	26 (45.6%)	28 (48.3%)	0.775
LCX	19 (33.3%)	18 (31.0%)	0.296
RCA	12 (21.1%)	12 (20.7%)	0.668
Left main disease	6 (10.5%)	6 (10.3%)	0.975
Lesion			
Type A	8 (14.0%)	7 (12.0%)	0.754
Type B	38 (66.7%)	40 (69.0%)	0.792
Type C	11 (19.3%)	11 (19.0%)	0.964
Drug-eluting stents	50 (87.7%)	51 (87.9%)	0.972
Thrombus in culprit vessel	36 (63.2%)	35 (60.3%)	0.756
Thrombus score			
Before PCI	2.6±0.5	2.8±0.7	0.683
After PCI	1.6±0.5	0.7±0.2	0.006
TIMI flow			
Before PCI (grade 0–1)	48 (84.2%)	48 (82.8%)	0.834
After PCI (grade 3)	41 (71.9%)	51 (89.7%)	0.016
TMPG			
Before PCI (grade 0–1)	51 (89.5%)	50 (86.2%)	0.802
After PCI (grade 3)	38 (66.7%)	49 (84.5%)	0.026
Distal embolism	8 (14.0%)	1 (1.7%)	0.035

LAD, left descending; LCX, left circumflex; RCA, right coronary artery; TIMI, Thrombolysis In Myocardial Infarction; TMPG, TIMI myocardial perfusion grade. Other abbreviation see in Table 1.

Table 3 The 14- and 30-Day MACE

	Control (n=57)	Study (n=58)	p value
LVEF (%)			
7-day	58.4±9.2	59.6±8.1	0.732
30-day	60.7±4.6	67.4±6.2	0.033
Composite 7-day MACE	10 (17.5%)	2 (3.5%)	0.030
Death	2	0	0.468
Non-fatal MI	1	0	0.993
Worsening HF	6	2	0.261
Revascularization	1	0	0.993
Composite 30-day MACE	4 (7.0%)	1 (1.7%)	0.350
Death	2	1	1.000
Non-fatal MI	1	0	0.993
Revascularization	1	0	0.993

MACE, major adverse cardiovascular events; LVEF, left ventricular ejection fraction; HF, heart failure. Other abbreviation see in Table 1.

Table 4 Complications at 14 Days After PCI

	Control (n=57)	Study (n=58)	p value
Major bleeding	5 (8.8%)	1 (1.7%)	0.201
Minor bleeding	4 (7.0%)	6 (10.3%)	0.763
Platelet reduction	3 (5.3%)	2 (3.5%)	0.984

Abbreviation see in Table 1.

TIMI flow grade and TMPG were higher (p=0.026 and 0.016, respectively). The incidence of distal embolism in the study group was also lower than in the control group (p=0.035, Table 2).

Clinical Outcomes

As shown in Table 3, there was no significant difference in LVEF between the 2 groups at 14 days after PCI (p=0.732). However, within 30 days of PCI, the average LVEF in the study group was higher than in the control group (p=0.033).

The MACE rate in the study group was lower than in the control group at 14 days following PCI (p=0.030, Table 3). However, there was no significant difference in the MACE rates of the 2 groups at 30 days after the PCI (p=0.350, Table 3).

Bleeding Complications and Platelet Reduction

There was no significant difference between the 2 groups in the major or minor bleeding rates (Table 4, p=0.201). Platelet reduction was found in 3 of the control and 2 of the study group patients (Table 4, p=0.984).

Discussion

The main findings of the present study are as follows.

(1) Intracoronary administration of tirofiban followed by intravenous infusion is associated with an improved TIMI flow and TMPG, and reduced thrombus scores following primary PCI.
(2) The intracoronary regimen is also associated with less MACE at 14 days after PCI, and improved left ventricular function at 30 days following PCI.
(3) Intracoronary administration of tirofiban does not appear to increase the risk of bleeding or platelet reduction.

To the best of our knowledge, this study is the first to demonstrate the safety and short-term efficacy of intracoronary bolus administration of tirofiban in patients with ACS. Previous studies of tirofiban have focused mostly on non-ST elevation ACS and their results have sometimes been inconsistent[7,15–17] The RESTORE investigators have shown in a large group of patients with unstable angina or acute MI that tirofiban reduced major cardiovascular events within 2 days following primary or nonprimary PCI; however, tirofiban did not improve the clinical outcomes or reduce coronary restenosis between day 2 and 6 months following the PCI[15,16] The TARGET trial, which also involved patients with unstable angina or non-ST-elevation MI, demonstrated that abciximab was superior to tirofiban in lowering the rates of MI at 30 days and 6 months; however, the 6-month mortality rates were identical for the abciximab and tirofiban groups[17] In a more recent study of ST-segment elevation ACS, a double-bolus intravenous regimen of tirofiban did not demonstrate significant angiographic or clinical outcomes in patients undergoing PCI[18]

The 30-day ventricular function and cardiac events following primary PCI are determined by a number of factors, such as the size of the infarct, the status of coronary reperfusion, the use of medications, and presence of serum inflammatory factors such as interleukin-10[1,2,19] In the present study, there were no significant differences between the study and the control groups in the baseline patient characteristics, plasma levels of CK-MB and cTnT, the time interval from onset of chest pain to PCI or the use of medications. The LVEF in the study group was higher than in the control group 30 days following PCI. These results suggest that intracoronary tirofiban may improve left ventricular function through its beneficial effects on coronary flow and myocardial perfusion soon after successful PCI.

In the present study more than 60% of patients had ST-elevation ACS. Intracoronary tirofiban was administered immediately before PCI because we hypothesized that local administration of a IIb/IIIa antagonist would have a faster and more efficient action on the coronary thrombus and vascular endothelium than the conventional intravenous bolus injection. In comparison with the control group, the study group showed a 14% reduction in the composite MACE within 14 days of primary PCI. Although there was no significant difference in the MACE rates within 30 days of PCI, a higher average LVEF was observed in the intracoronary tirofiban group, suggesting an improvement in left ventricular function.

Study Limitations

The first is that the number of patients was relatively small, so it was not possible for us to perform a subgroup analysis and compare the effects of intracoronary tirofiban on ST-elevation and non-ST elevation ACS. In addition, although we purposefully recruited elderly patients to evaluate the bleeding rates and platelet reduction in this population, the clinical benefits of intracoronary tirofiban observed in this study may or may not be applicable to a younger patient population.

In conclusion, intracoronary bolus injection of tirofiban appears superior to intravenous bolus administration in reducing short-term MACE and improving coronary flow or myocardial perfusion following primary PCI. At 30 days after intracoronary tirofiban administration and PCI there was a significant improvement in left ventricular function. Further studies in a larger patient population are required to evaluate the long-term effect of intracoronary tirofiban on the outcomes of ACS following PCI.

References

1. Acute Coronary Syndrome Guidelines Working Group. Guidelines for the management of acute coronary syndromes 2006. *Med J Aust* 2006; **184:** S1–S32.
2. King SB III, Smith SC Jr, Hirshfeld JW Jr, Jacobs AK, Morrison DA, Williams DO. 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: 2007 Writing Group to Review New Evidence and Update the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention, Writing on Behalf of the 2005 Writing Committee. *Circulation* 2008; **117:** 261–295.
3. Topol EJ, Neumann FJ, Montalescot G. A preferred reperfusion strategy for acute myocardial infarction. *J Am Coll Cardiol* 2003; **42:** 1886–1889.
4. Kabbani SS, Aggarwal A, Terrien EF, DiBattiste PM, Sobel BE, Schneider DJ. Sub-optimal early inhibition of platelets by treatment with tirofiban and implications for coronary interventions. *Am J Cardiol* 2002; **89:** 647–650.
5. Schneider DJ, Herrmann HC, Lakkis N, Aguirre F, Lo MW, Yin KC, et al. Increased concentrations of tirofiban in blood and their correlation with inhibition of platelet aggregation after greater bolus doses of tirofiban. *Am J Cardiol* 2003; **91:** 334–336.
6. Valgimigli M, Percolo G, Barbieri D, Ferrari F, Guardigli G, Parrinello G, et al. The additive value of tirofiban administered with the high-dose bolus in the prevention of ischemic complications during high-risk coronary angioplasty (the ADVANCE trial). *J Am Coll Cardiol* 2004; **44:** 14–19.
7. Bolognese L, Falsini G, Liistro F, Angioli P, Ducci K, Taddei T, et al. Randomized comparison of upstream tirofiban versus downstream high bolus dose tirofiban or abciximab on tissue-level perfusion and troponin release in high-risk acute coronary syndromes treated with percutaneous coronary interventions. *J Am Coll Cardiol* 2006; **47:** 522–528.
8. Wöhrle J, Grebe OC, Nusser T, Al-Khayer E, Schaible S, Kochs M, et al. Reduction of major adverse cardiac events with intracoronary compared with intravenous bolus application of abciximab in patients with acute myocardial infarction or unstable angina undergoing coronary angioplasty. *Circulation* 2003; **107:** 1840–1843.
9. Romagnoli E, Burzotta F, Trani C, Biondi-Zoccai GG, Giannico F, Crea F. Rationale for intracoronary administration of abciximab. *J Thromb Thrombolysis* 2007; **23:** 57–63.
10. Heer T, Zeymer U, Juenger C, Gitt AK, Wienbergen H, Zahn R, et al; Acute Coronary Syndromes Registry Investigators. Beneficial effects of abciximab in patients with primary percutaneous intervention for acute ST segment elevation myocardial infarction in clinical practice. *Heart* 2006; **92:** 1484–1489.
11. Tan K, Sulke N, Taub N, Sowton E. Clinical and lesion morphologic determinants of coronary angioplasty success and complications: Current experience. *J Am Coll Cardiol* 1995; **25:** 855–865.
12. TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial: Phase I findings. *N Engl J Med* 1985; **312:** 932–936.
13. Gibson CM, Cannon CP, Murphy SA, Ryan KA, Mesley R, Marble SJ, et al. Relationship of TIMI myocardial perfusion grade to mortality after administration of thrombolytic drugs. *Circulation* 2000; **101:** 125–130.
14. Kalaria VG, Rouch C, Bourdillon PD, Breall JA. Distal emboli protection in patients undergoing percutaneous coronary intervention after a recent myocardial infarction. *Catheter Cardiovasc Interv* 2002; **57:** 54–60.
15. The RESTORE Investigators. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary

angioplasty: Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis. *Circulation* 1997; **96:** 1445–1453.
16. Gibson CM, Goel M, Cohen DJ, Piana RN, Deckelbaum LI, Harris KE, et al. Six-month angiographic and clinical follow-up of patients prospectively randomized to receive either tirofiban or placebo during angioplasty in the RESTORE trial (Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis). *J Am Coll Cardiol* 1998; **32:** 28–34.
17. Stone GW, Moliterno DJ, Bertrand M, Neumann FJ, Herrmann HC, Powers ER, et al. Impact of clinical syndrome acuity on the differential response to 2 glycoprotein IIb/IIIa inhibitors in patients undergoing coronary stenting: The TARGET Trial. *Circulation* 2002; **105:** 2347–2354.
18. Chen SM, Hsieh YK, Guo GB, Fang CY, Yip HK, Wu CJ, et al. Angiographic and clinical outcome in ST-segment elevation myocardial infarction patients receiving an adjunctive double bolus regimen of tirofiban for primary percutaneous coronary intervention. *Circ J* 2006; **70:** 536–541.
19. Yip HK, Youssef AA, Chang LT, Yang CH, Sheu JJ, Chua S, et al. Association of interleukin-10 level with increased 30-day mortality in patients with ST-segment elevation acute myocardial infarction undergoing primary coronary intervention. *Circ J* 2007; **71:** 1086–1091.